## 1. Scientific Abstract

There has been increasing interest in recent years in developing immunologic approaches to malignancies, and there is good evidence that the growth of renal cell carcinoma (RCC) can be modulated by the host's immune system. In fact the use of the immunomodulatory cytokine interleukin-2 (IL-2) is approved treatment for this disease. The efficacy of this approach remains low, and there is no other reasonable conventional therapy for patients with metastatic RCC. Therefore there is a need to develop novel treatment strategies. The development of autologous tumor cell vaccines, genetically modified to render them more immunogenic is an approach that is actively being studied. One of the genetic manipulations that is being employed by several groups is to overexpress B7-1 to provide co-stimulation to tumor-reactive T cells. The rationale for this is that in order to mount a cytotoxic response, T cells need two signals: the binding of the T cell receptor (TCR) to an antigenic peptide presented on MHC, and the binding of CD28 to B7-1. Since B7-1 is not normally expressed by RCC cells, the forced expression by transfection of an exogenous B7-1 gene could make the tumor cells more immunogenic. This has been shown to be the case in mice where the injection of tumor cells transfected with B7-1 can result in the T cell mediated rejection of unmanipulated parental tumor cells.

Patients enrolled on this phase I protocol will be treated with autologous tumor cells modified to express B7-1 which will function as a tumor vaccine. Primary tumors or metastases will be resected from patients with stage IV RCC. The tumor cells will be adapted to in vitro culture; infected with a recombinant adenoviral vector containing the human B7-1 cDNA driven by the CMV promoter; radiated; and stored in liquid nitrogen. Aliquots of the B7-1 gene-modified tumor cells will be administered to the patients as a vaccine at varying intervals according to the dose escalation scheme. The patients will also receive systemic IL-2 for the dual purpose of providing accepted therapy for this disease as well as expanding the tumor-reactive T cells activated by the vaccine. The immunogenicity and toxicity of the vaccine, as well as the clinical response will be assessed in three to five patients at each of three dose levels.